PCT/EP 99 / 08704

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Signed Andrew Gersey

Dated 1 November 1999

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Patents Form 1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — KR/JW/P32313

2. Patent application number
(The Pt
9912191.5 — 25 MAY 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

SmithKline Beecham plc
New Horizons Court, Brentford, Middx TW8 9EP,
Great Britain

Patents ADP number *(if you know it)*

5800974002

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — Novel Composition and Use

5. Name of your agent *(if you have one)*

CORPORATE INTELLECTUAL PROPERTY

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

Patents ADP number *(if you know it)*

5800974004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	6
Claim(s)	
Abstract	
Drawings	

10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 1/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature K Rutter Date 25-May-99

12. Name and daytime telephone number of person to contact in the United Kingdom: K Rutter 01279 644396

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Notes

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NOVEL COMPOSITION AND USE

This invention relates to a novel composition, in particular to a modified release composition and it use in medicine, especially its use for the treatment of diabetes mellitus, preferably Type 2 diabetes, and conditions associated with diabetes mellitus.

Alpha glucosidase inhibitor antihyperglycaemic agents, such as acarbose, emiglitate and miglitol, are commonly used in the treatment of NIDDM (or Type II diabetes).

European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter 'Compound (I)'). WO94/05659 discloses certain salts of Compound (I) including the maleate salt at example 1 thereof.

Compound (I) is an example of a class of anti-hyperglycaemic agents known as 'insulin sensitisers'. In particular Compound (I) is a thiazolidinedione insulin sensitiser.

European Patent Applications, Publication Numbers: 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734, 0508740; International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and United States Patent Numbers 5104888 and 5478852, also disclose certain thiazolidinedione insulin sensitisers.

Another series of compounds generally recognised as having insulin sensitiser activity are those typified by the compounds disclosed in International Patent Applications, Publication Numbers WO93/21166 and WO94/01420. These compounds are herein referred to as 'acyclic insulin sensitisers'. Other examples of acyclic insulin sensitisers are those disclosed in United States Patent Number 5232945 and International Patent Applications, Publication Numbers WO92/03425 and WO91/19702.

Examples of other insulin sensitisers are those disclosed in European Patent Application, Publication Number 0533933, Japanese Patent Application Publication Number 05271204 and United States Patent Number 5264451.

The above mentioned publications are incorporated herein by reference.

It is now indicated that certain modified release pharmaceutical compositions allow administration of a single daily dose of Compound (I) and an alpha glucosidase inhibitor which provide an advantageous delivery of drug for maintaining effective glycaemic control with no observed adverse side effects. Such combination is therefore particularly useful for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus.

Accordingly, the invention provides a modified release pharmaceutical composition, suitably for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus in a mammal, such as a human, which composition comprises: an insulin sensitiser, such as Compound (I), an alpha glucosidase inhibitor antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor, wherein the carrier is arranged to provide a modified release of the active agents.

Suitably the modified release is a delayed release.

Delayed release is suitably obtained by use of a tablet coated with a gastric-resistant polymer, for example Eudragit L100-55.

Suitably the modified release is a sustained release, for example providing effective release of active agents over a time period of up to 26 hours.

Sustained release is suitably obtained by use of a non-disintegrating matrix tablet formulation, for example by incorporating Eudragit RS into the tablet.

Sustained release can also be achieved by using a semi-permeable membrane coated tablet, for example by applying Eudragit RS to a tablet.

Suitably the modified release is a pulsed release, for example providing two pulses of release of active agents per 24 hours.

In addition the invention envisages the combination of pulsed, delayed and/or sustained release for each or both active agents, thereby enabling for example the release of the reagents at different times.

Usually the compositions are adapted for oral administration. However, they may be adapted for other modes of administration, for example parenteral administration, sublingual or transdermal administration.

A suitable alpha glucosidase inhibitor antihyperglycaemic agent is acarbose.

Other suitable alpha glucosidase inhibitor antihyperglycaemic agents are Emiglitate and Miglitol.

A suitable thiazolidinedione insulin sensitiser is Compound (I).

Other suitable thiazolidinedione insulin sensitisers include (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl)thiazolidine-2,4-dione (or englitazone).

Suitable unit dosages of the insulin sensitiser and the alpha glucosidase inhibitor antihyperglycaemic agent, such as acarbose, include the known permissible doses for these compounds as described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example

see the 31st Edition page 341 and pages cited therein) or the above mentioned publications.

The dosages of each particular active agent in any given composition can as required vary within a range of doses known to be required in respect accepted dosage regimens for that compound. Dosages of each active agent can also be adapted as required to take into account advantageous effects of combining the agents as mention herein.

In one particular aspect, the composition comprises 2 to 12 mg of Compound (I).

Suitable the composition comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I).

Particularly, the composition comprises 2 to 4 , 4 to 8 or 8 to 12 mg of Compound (I).

Particularly, the composition comprises 2 to 4mg of Compound (I).

Particularly, the composition comprises 4 to 8mg of Compound (I).

Particularly, the composition comprises 8 to 12 mg of Compound (I).

Preferably, the composition comprises 2 mg of Compound (I).

Preferably, the composition comprises 4 mg of Compound (I).

Preferably, the composition comprises 8 mg of Compound (I).

Suitable unit dosages of other insulin sensitisers include from 100 to 800mg of troglitazone such as 200, 400 or 800mg or from 10 to 40mg of pioglitazone such as 20, 30 or 40 mg.

A suitable amount of acarbose is in the range of from 50 to 600 mg, for example 100mg or 200mg.

The compounds mentioned herein, in particular the thiazolidinediones such as Compound (I), may exist in one of several tautomeric forms, all of which are encompassed by the invention as individual tautomeric forms or as mixtures thereof. The compounds mentioned herein may contain one or more chiral carbon atoms and hence can exist in two or more stereoisomeric forms, all of which are encompassed by the invention either as individual isomers or as mixtures of isomers, including racemates.

It will be understood that the insulin sensitiser, such as Compound (I) and the alpha glucosidase inhibitor antihyperglycaemic agent are each administered in a pharmaceutically acceptable form, including pharmaceutically acceptable derivatives such as pharmaceutically acceptable salts, esters and solvates thereof, as appropriate of the relevant pharmaceutically active agent. In certain instances herein the names used for the relevant alpha glucosidase inhibitor may relate to a particular pharmaceutical form of the relevant active agent: It will be understood that all pharmaceutically acceptable forms of the active agents per se are encompassed by this invention.

Suitable pharmaceutically acceptable forms of the insulin sensitiser and alpha glucosidase inhibitor antihyperglycaemic agent depend upon the particular agent used but includes known pharmaceutically acceptable forms of the particular compound chosen. Such derivatives are found or are referred to in standard reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and the above mentioned publications.

Suitable pharmaceutically acceptable forms of Compound (I) include those described in EP 0306228 and WO94/05659, especially pharmaceutically acceptable salted or solvated forms. A preferred pharmaceutically acceptable salt is a maleate. A preferred pharmaceutically acceptable solvated form is a hydrate.

The insulin sensitiser or the alpha glucosidase inhibitor antihyperglycaemic agent of choice is prepared according to known methods, such methods are found or are referred to in standard reference texts, such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or as described in the above mentioned publications.

Compound (I) or, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in EP 0306228 and WO94/05659. The disclosures of EP 0306228 and WO94/05659 are incorporated herein by reference.

When used herein the term 'conditions associated with diabetes' includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

When used herein the term 'conditions associated with the pre-diabetic state' includes conditions such as insulin resistance, including hereditary insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

'Conditions associated with diabetes mellitus itself' include hyperglycaemia, insulin resistance, including acquired insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational diabetes.

'Complications associated with diabetes mellitus' includes renal disease, especially renal disease associated with Type 2 diabetes, neuropathy and retinopathy.

Renal diseases associated with Type 2 diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As used herein the term 'pharmaceutically acceptable' embraces both human and veterinary use: for example the term 'pharmaceutically acceptable' embraces a veterinarily acceptable compound.

For the avoidance of doubt, when reference is made herein to scalar amounts, including mg amounts, of Compound (I) in a pharmaceutically acceptable form, the scalar amount referred to is made in respect of Compound (I) *per se*: For example 2 mg of Compound (I) in the form of the maleate salt is that amount of maleate salt which contains 2 mg of Compound (I).

Diabetes mellitus is preferably Type 2 diabetes.

The particularly beneficial effect on glycaemic control provided by the treatment of the invention is indicated to be a synergistic effect relative to the control expected for the sum of the effects of the individual active agents.

Glycaemic control may be characterised using conventional methods, for example by measurement of a typically used index of glycaemic control such as fasting plasma glucose or glycosylated haemoglobin (Hb A1c). Such indices are determined using standard methodology, for example those described in: Tuescher A, Richterich, P., Schweiz. med. Wschr. 101 (1971), 345 and 390 and Frank P., 'Monitoring the Diabetic Patent with Glycosolated Hemoglobin Measurements', Clinical Products 1988.

In a preferred aspect, the dosage level of each of the active agents when used in accordance with the treatment of the invention will be less than would have been required from a purely additive effect upon glycaemic control.

There is also an indication that the treatment of the invention will effect an improvement, relative to the individual agents, in the levels of advanced glycosylation end products (AGEs), leptin and serum lipids including total cholesterol, HDL-cholesterol, LDL-cholesterol including improvements in the ratios thereof, in particular an improvement in serum lipids including total cholesterol, HDL-cholesterol, LDL-cholesterol including improvements in the ratios thereof.

Usually the compositions are adapted for oral administration. However, they may be adapted for other modes of administration, for example transdermal administration.

The compositions are formulated to provide the modified release of active agents according to the appropriate methods disclosed in Sustained and Controlled Release Drug Delivery Systems, Editor Joe R Robinson, Volume 7, published by Marcel Dekker under the title Drugs and the Pharmaceutical Sciences, Controlled Drug Delivery, 2nd Edition' edited by Joe Robinson and Vince Lee, Marcel Dekker, 1987 and 'Drug Delivery to the Gastrointestinal Tract' Editors: J G Hardy, S S. Davis and C G Wilson also with reference to texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The

Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and Harry's Cosmeticology (Leonard Hill Books).

Preferably, the compositions are in unit dosage form. Unit dose presentation forms for oral administration may be in tablet or capsule form and may as necessary contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

As required the solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Compositions may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

No adverse toxicological effects are expected for the compositions of the invention in the above mentioned dosage ranges.